International Journal of Cardiology 164 (2013) 64–69

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Prolonged beneficial effect of bosentan treatment and 4-year survival rates in adult patients with pulmonary arterial hypertension associated with congenital heart disease

Jeroen C. Vis [a,b], Marielle G. Duffels [a], Pepijn Mulder [a], Rianne H.A.C.M. de Bruin-Bon [a], Berto J. Bouma [a], Rolf M.F. Berger [c], Elke S. Hoendermis [c], Arie P.J. van Dijk [d], Barbara J.M. Mulder [a,b,*]

[a] Department of Cardiology, Academic Medical Centre, Amsterdam, The Netherlands
[b] Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands
[c] Department of Cardiology, University Medical Centre Groningen, Groningen, The Netherlands
[d] Department of Cardiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 12 February 2011
Received in revised form 20 May 2011
Accepted 10 June 2011
Available online 1 July 2011

Keywords:
Pulmonary arterial hypertension
Congenital heart disease
Advanced therapy
Survival

ABSTRACT

Pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) due to systemic to pulmonary shunting is associated with a high risk of morbidity and mortality. In this study we evaluated 4 years treatment effect of bosentan on exercise capacity and quality of life and survival rates in 64 adult patients with PAH associated with CHD, including patients with Down syndrome (DS). All patients were evaluated at baseline and during follow-up with laboratory tests, 6-minute walk test, quality of life questionnaires, and Doppler echocardiography. In total, 13 patients (20%) died during 4-years of follow-up; 4 patients with DS and 9 patients without DS. Mean follow-up of all patients treated with bosentan was 3.5 ± 1.2 year. We analyzed treatment efficacy separately within patients without DS (n = 34) and patients with DS (n = 30). Mean 6-minute walking distance (6MWD) in patients without DS significantly increased at 6 months from 417 ± 108 to 458 ± 104 m (+41 m; p = 0.002) and significant improvement continued to exist during at least 2.5 years of follow-up (p = 0.003). Moreover, stroke volume increased significantly (p = 0.02). In the patients with DS, 6-MWD, stroke volume and quality of life remained stable during treatment. In this study we demonstrate a prolonged beneficial effect of bosentan treatment on exercise capacity, stroke volume and quality of life in patients without DS. However the mortality rate of 20% of patients after 4 years of follow-up remains high.

1. Introduction

Pulmonary arterial hypertension (PAH) is a rare syndrome of dyspnoea, fatigue, chest pain and syncope caused by a progressive increase in pulmonary vascular resistance and defined by a sustained elevation of pulmonary arterial pressure to more than 25 mm Hg at rest and a capillary wedge pressure of 15 mm Hg or less [1]. It is clinically characterised by decreased functional capacity, right ventricular failure and a shortened life expectancy [2,3]. PAH due to congenital heart disease (CHD) with systemic to pulmonary shunt is a major subgroup of patients with PAH [4]. CHD–PAH is a result of systemic to pulmonary shunting and chronic increased flow that ultimately results in adaptations of pulmonary vasculature and endothelial dysfunction. The advanced stage is called Eisenmenger syndrome which forms a small percentage (1%) of all CHD patients [5]. Until recently, treatment options for patients with pulmonary arterial hypertension were limited. A major breakthrough in the treatment of patients with PAH has been the introduction of the oral endothelin receptor antagonist bosentan. Short-term treatment with bosentan has shown to improve morbidity of patients with PAH, including those with Eisenmenger syndrome [6]. However, results on longer-term treatment response are equivocal and data on quality of life is limited despite the importance of quality of life assessment [7,8]. Although several studies reported a persistent beneficial effect of bosentan on exercise capacity [9–13], other studies reported a gradual decline of exercise capacity to baseline values after 2 years of bosentan treatment [14–17]. In patients with Down syndrome (DS), the treatment effect of bosentan is largely unknown [18]. The aim of our study was to evaluate the long-term efficacy of bosentan treatment and 4 years survival rates of adult patients with PAH associated with CHD with and without the DS.

* Corresponding author at: Department of Cardiology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 5662193; fax: +31 20 5666809.
E-mail address: b.j.mulder@amc.uva.nl (B.J.M. Mulder).

0167-5273
doi:10.1016/j.ijcard.2011.06.064

2. Methods

2.1. Study population

Adult patients with Eisenmenger syndrome and the following congenital heart defects were included: septal defects, patent arterial duct and created aortopulmonary shunts in cyanotic congenital heart disease (Waterston/Potts shunt). Patients with persistent PAH after previous closure of their CHD defect were also enrolled. Other criterion to receive bosentan therapy was proven PAH by right heart catheterisation in the past with symptoms affecting quality of life (patients in NYHA class 2 to 4). To exclude other causes of PAH, lung function tests (spirometry, forced expiratory volume in 1 second, and forced vital capacity) were obtained at baseline. PAH was defined as a mean pulmonary arterial pressure of more than 25 mm Hg at rest. Patients receiving prostacyclin, phosphodiesterase type 5 inhibitor, glibenclamide or cyclosporine before study inclusion and patients with obstruction of the right ventricular outflow tract, pulmonary valve, or pulmonary arteries were excluded. Patients were divided into 2 groups: patients without DS and patients with DS.

2.2. Study design

All patients were evaluated according to a standardized treatment protocol with clinical examination (determination of functional class) Doppler echocardiography, a six-minute walk test (6MWT), laboratory tests (including haemoglobin, creatinine, uric acid, and N-terminal pro-B natriuretic peptide (NT-pro-BNP)) and quality of life questionnaires These tests (except for echocardiogram) were administered at baseline and after 3, 6, 9 and 12 months follow-up and from then on twice yearly. All tests were performed on the same day. Data on events such as death were taken from the databases of the participating hospitals.

Submaximal exercise capacity was assessed using the 6-MWT, according to the guidelines of the American Thoracic Society with continuous pulse oximetry monitoring [19]. To exclude the effect of a learning curve, the 6-MWD at baseline was performed twice, using the second test as baseline value. In previous research, the 6MWT appeared to be an invalid test to examine exercise capacity in patients with DS [20]. Therefore in this study 6MWTs were not analyzed to investigate treatment effect in patients with DS.

Doppler echocardiography (VIVID 7 General Electric, USA) was performed to evaluate left and right ventricular function during bosentan treatment at baseline and then yearly. When possible, right ventricular function was measured by tricuspid annular plane systolic excursion and the systolic pulmonary arterial pressure was estimated by the peak velocity of the tricuspid regurgitation jet using continuous-wave Doppler and the pressure off the right atrium, measured by the collapse of the inferior vena cava. To establish PAH diagnosis, minimal systolic pulmonary arterial pressure had to be 40 mm Hg at rest with a tricuspid regurgitation velocity of more than 2.8 m/s, according to the guidelines of the European Society of Cardiology [1]. In patients without complex cardiac geometry, TEI index and contraction duration of the right ventricle were assessed using tissue Doppler imaging. Right ventricular contraction duration, corrected for heart rate, was measured from the onset of the QRS complex to the onset of early diastolic filling of the right ventricle (E). Left ventricular stroke volume was assessed by early systolic measurement of the left ventricular outflow tract diameter (LVOTd), in parasternal long axis view and the velocity time integral (VTI) in apical long axis view by pulsed wave (PW) Doppler. The PW sample volume was positioned just proximal the aortic valve leaflets, within the left ventricular outflow tract. The VTI was measured by tracing the leading edge of the velocity spectrum. Stroke volume was calculated according the following formula: $Area\ (A) = (LVOTd/2)^2 \times \pi$; $Stroke\ volume\ (SV) = A \times VTI$. All echocardiographic images were acquired and recorded digitally, and analyzed offline by a single observer (RB).

Quality of life was evaluated by means of the SF-36 questionnaire. The SF-36 is a well-documented, widely used and validated, self-administered quality of life scoring system incorporating 36 questions. It includes 8 independent scales (scored as a number between 0 and 100) that assess the following general health concepts: physical functioning, limitations because of physical health problems (role physical), bodily pain, general health perceptions, vitality, social functioning, limitations because of emotional problems (role emotional), and mental health. In patients with DS a close caretaker or parent was asked to fill out the questionnaire on behalf of the subject.

2.3. Statistical analysis

Descriptive data are presented as mean with standard deviation if normally distributed or as median with range, as appropriate. Comparisons from baseline to each consecutive follow-up visit were assessed by paired student t tests. Data for the SF-36 were summarized by mean change from baseline to each time-point for the patients observed. A value of $p<0.05$ was considered to be significant. As NT-pro-BNP levels were apparently not normally distributed, statistical analyses were performed on logarithmically transformed values. Differences of group means and of interval-to-interval comparisons were analyzed. Logarithmic transformation of the NT-pro-BNP levels resulted in the bell-shaped distribution. Cox regression analyses was performed to identify independent predictors for survival (sex, underlying CHD, DS, Eisenmenger syndrome, age, baseline 6MWD, cardiac output, and NT-pro-BNP). The Wilcoxon signed-rank test was used to compare the change in NYHA class from baseline to end-of-study. Death was scored as NYHA class 5. Statistical analysis was performed with SPSS 16.0.

3. Results

3.1. Baseline characteristics

Between January 2005 and July 2010, 70 patients were enrolled in the treatment protocol. Overall, 64 patients (30 with DS) received bosentan and were included in this study. Four patients refused treatment initiation and reimbursement of bosentan by the health insurance was rejected in 2 patients. The median follow-up duration was 42 months (range 2 to 64 months). Table 1 summarizes patients' baseline characteristics. Of the 7 non-DS patients without Eisenmenger syndrome, 6 patients had persistent PAH after previous closure of their CHD and 1 patient had refused an operation. During follow-up only 1 patient was treated with concomitant therapy and sildenafil was started after 2.5 years follow-up on monotherapy with bosentan.

3.2. Survival analysis

In total, 13 people died during 4-years of follow-up, 4 patients with DS and 9 patients without DS. Table 2 shows detailed information about the deceased patients. Survival rates in patients without DS at 1-, 2-and 4-years were respectively 88%, 88% and 72%, and for patients with DS 97%, 93% and 80%. Fig. 1 shows the Kaplan–Meier survival

Table 1
Baseline characteristics of the study population.

	Patients without DS ($n=34$)	Patients with DS ($n=30$)	p-value
Age, years	46 ± 14	36 ± 10	0.001
Male gender, (%)	11 (32)	19 (63)	0.01
Eisenmenger syndrome, (%)	27 (79)	30 (100)	0.01
Median follow-up, months (range)	47 (2–64)	48 (13–60)	0.3
Underlying congenital heart defects			
Atrial septal defect primum	2	0	
Atrial septal defect secundum (closed)	6 (3)	0	
Atrial septal defect sinus venosus	2	0	
Atrial septal defect + ventricular septal defect	2	0	
Ventricular septal defect (closed)	8 (2)	7	
Ventricular septal defect + patent ductus arteriosus	2	3	
Ventricular septal defect + atresic pulmonary artery	2	0	
Ventricular septal defect + right pulmonary artery from ascending aorta	1	0	
Closed patent ductus arteriosus	1	1	
Double inlet left ventricle + patent ductus arteriosus	2	0	
Tetralogy of fallot + Potts anastomosis	1	0	
Univentricular heart	3	0	
Discordant ventriculo-arterial connection with ventricular septal defect	2	0	
Atrioventricular septal defect	0	18	
Atrioventricular septal defect + patent ductus arteriosus	0	1	
NYHA functional class			
II	4	8	
III	28	20	
IV	2	2	
Oxygen saturation, (%)	85 ± 8	84 ± 8	0.5
Six-minute walk distance at baseline, m	401 ± 112		
Systolic pulmonary arterial pressure, mm Hg	83 ± 23	93 ± 11	0.1
Stroke volume, ml	72 ± 25	67 ± 32	0.6
Cardiac output, L/min	5.3 ± 1.5	4.9 ± 2.2	0.5
NT-pro-BNP, ng/L	1457 ± 2094	774 ± 956	0.1
Creatinine, μmol/L	80 ± 28	94 ± 30	0.08
Uric acid, mmol/L	0.4 ± 0.1	0.5 ± 01	0.1
Haemoglobin, mmol/L	11 ± 2	13 ± 2	0.001

Mean values with standard deviation. NYHA; New York Heart Association.

Table 2
Mortality.

Deceased	Male	Down syndrome	NYHA (baseline)	Follow-up (months)	Age at death (years)	Cause of death	Congenital heart defect
Patient 1	0	0	3	2	49	Unknown	Double inlet left ventricle + patent arterial duct
Patient 2	1	0	3	4	38	Sudden death	Ventricular septal defect
Patient 3	1	0	3	5	44	Sudden death	Atrial septal defect + ventricular septal defect
Patient 4	0	0	3	5	76	Right heart failure	Atrial septal defect secundum
Patient 5	1	1	2	13	30	Brain abscess	Atrioventricular septal defect
Patient 6	0	1	4	20	28	Unknown	Atrioventricular septal defect
Patient 7	1	0	3	32	75	Right heart failure	Atrial septal defect primum
Patient 8	0	1	3	36	56	Right heart failure	Ventricular septal defect
Patient 9	1	0	3	38	26	Sudden death	Ventricular septal defect
Patient 10	0	0	3	46	38	Right heart failure	Discordant + ventriculo-arterial connection + ventricular septal defect
Patient 11	0	0	3	48	65	Right heart failure	Ventricular septal defect
Patient 12	1	1	2	50	34	Right heart failure	Atrioventricular septal defect
Patient 13	1	0	4	55	52	Unknown	Atrial septal defect secundum

NYHA; New York Heart Association.

curve of the two patient groups. Mean survival time was 4.3 ± 0.3 year in patients without DS and 4.6 ± 0.2 year in patients with DS. No significant independent predictors for survival were found. Underlying cardiac defect did not influence survival outcome. Even so, patients with Eisenmenger syndrome had no better survival compared to patients with persistent PAH after shunt closure ($p = 0.5$).

3.3. Six-minute walk test

Bosentan showed a prolonged significant improvement of the 6MWD in the patient group without DS (see Fig. 2). The mean 6MWD maximally increased with +41 m from 417 ± 108 to 458 ± 104 m ($p = 0.002$) at 6 months of treatment and remained increased with +36 m after 2.5 years of follow-up ($p = 0.003$). Afterwards, improvement of 6MWD was still observed although not statistically significant ($p = 0.2$) in the smaller patient population. The majority ($n = 6$) of the 9 deceased patients without DS showed initial improvement of 6MWD at 3 months. Two patients had no response and 1 patient died before first follow-up visit at 3 months.

Mean resting heart rate at baseline (85 ± 12 bpm) decreased significantly during follow-up. Mean reduction was 6, 7, 12 and 12 bpm at respectively 1 year ($p = 0.02$), 2 year ($p = 0.03$), 3 year ($p = 0.01$) and 4 year ($p = 0.04$) follow-up. The mean maximum heart rate during the 6MWT did not change significantly during follow-up compared to baseline (111 ± 17 bpm). Mean resting oxygen saturation at baseline was 88% and did not change significantly during 4 years follow-up. The mean minimum oxygen saturation during the 6MWT was 71% and no significant improvement was found during follow-up.

3.4. Echocardiography

Echocardiographic parameters at baseline and during treatment are shown in Table 3. In general, most echocardiographic parameters remained unchanged in both groups of patients during follow-up. However, analyses of the left ventricle in patients without DS showed that mean stroke volume significantly increased (+13.5 ml) after 3 years follow-up ($p = 0.02$). Even so, mean cardiac output tended to increase without reaching significance.

3.5. Laboratory testing

Baseline levels of laboratory test are shown in Table 1. The mean logNT-pro-BNP level decreased significantly from 2.8 ± 0.5 to 2.7 m ± 0.5 ng/L ($p = 0.03$) at 3 months, at 6 months ($p = 0.02$) and 1 year ($p = 0.05$) of treatment (see Fig. 3). After 1 year follow-up, logNT-pro-BNP levels returned to baseline levels and tended to deteriorate (although not statistically significantly). Haemoglobin, creatinine and uric acid levels did not change significantly. No correlation could be found between baseline 6MWD or change in 6MWD during bosentan treatment and baseline logNT-pro-BNP. In addition, no relations were

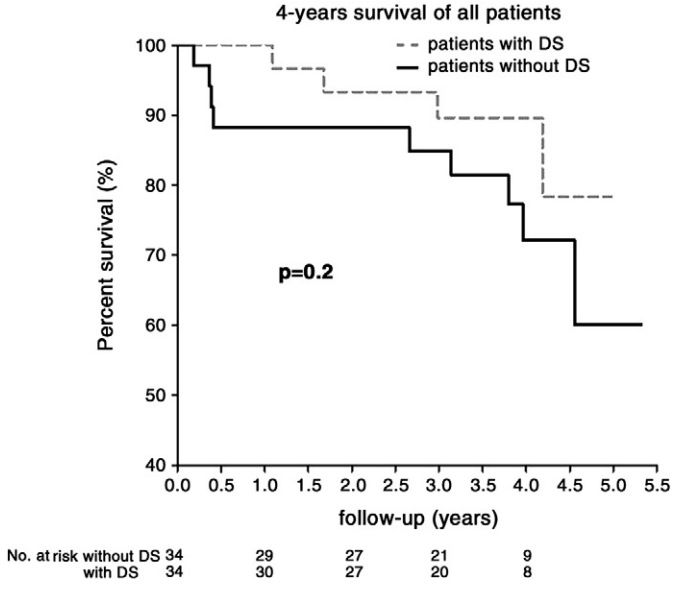

Fig. 1. 4-years survival of all patients. DS; Down syndrome.

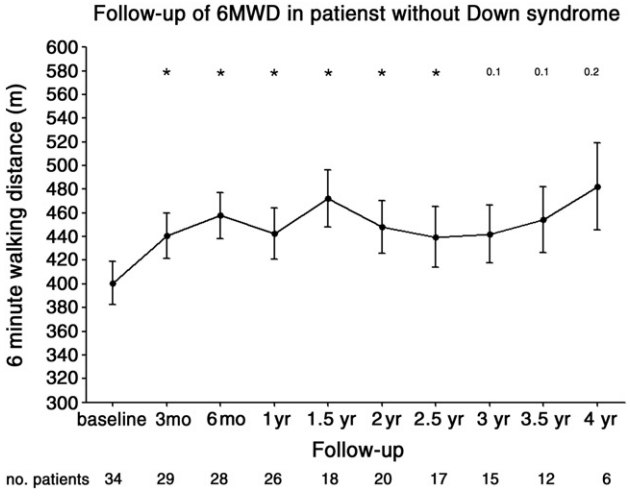

Fig. 2. 6MWD in patients without DS during follow-up. DS; Down syndrome.

Table 3
Echocardiography parameters during follow-up.

Non Down syndrome	Baseline	Δ 1 year FU	*p*-value	Δ 2 year FU	*p*-value	Δ>3 year FU	*p*-value
Heart rate, bpm	78±11	−0.1	1.0	−3.1	0.3	−5.0	0.1
Stroke volume, ml	72.3±25.9	8.5	0.06	7.8	0.4	13.5	0.02
Cardiac output, L/min	5.5±1.6	0.7	0.2	0.6	0.4	0.6	0.1
TEI index	0.5±0.2	0.03	0.6	0.06	0.6	0.10	0.1
Tricuspid annular plane systolic excursion, cm	1.9±0.6	−0.1	0.9	1.2	0.4	1.0	0.6
Pulmonary arterial pressure, mm Hg	84±23	−3.0	0.6	−6.4	0.2	−4.5	0.3
Down syndrome							
Heart rate, bpm	75±12	1.1	0.7	−2.8	0.4	0.9	0.8
Stroke volume, ml	68.9±37.0	5.4	0.2	7.3	0.1	−1.9	0.8
Cardiac output, L/min	5.1±2.5	0.4	0.3	0.2	0.5	−0.1	0.8
TEI index	0.6±0.2	0	0.9	−0.06	0.3	−0.05	0.4
Tricuspid annular plane systolic excursion, cm	1.9±0.4	0.9	0.4	−0.5	0.7	0.6	0.4
Pulmonary arterial pressure, mm Hg	97±16	−7.3	0.05	−5.2	0.2	−3.7	0.4

Mean values with standard deviation. *p*-values are analyses compared to baseline; FU, follow-up; bpm, beats per minute; FU, follow-up.
TEI index is a combined myocardial performance index (isovolumic contraction time plus isovolumic relaxation time divided by ejection time).

found between changes in 6MWD and haemoglobin, creatinine or uric acid levels.

3.6. Quality of life

Quality of life improved significantly in 2 of the 8 scales assessed by the SF-36, as shown in Fig. 4a and b. Daily life limitations caused by physical health problems (role physical) improved significantly compared to baseline and the improvement seemed to persist during longer-term follow-up (Fig. 4a). In addition, physical functioning improved significantly after 3 months and the improvement remained until 3 years of bosentan treatment (Fig. 4b). In patients with DS, all 8 scales of the SF-36 showed no significant improvement of quality of life.

3.7. NYHA classification

NYHA classification was assessed at baseline and at the end-of-study visit. The majority of patients were in NYHA class III at baseline. NYHA class had improved in 23% of patients, had deteriorated in 25% of patients and had remained stable in 52% of patients (see Table 4). NYHA class did not change significantly during follow-up ($p = 0.07$).

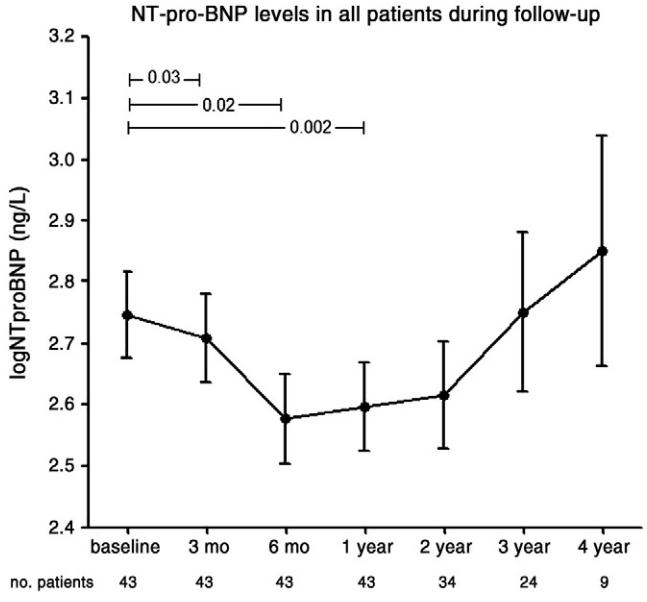

Fig. 3. NT-pro-BNP level in all patients during follow-up. NT-pro-BNP; N-terminal pro-B natriuretic peptide.

Although a trend towards worsening in NYHA class was shown in patients without DS.

3.8. Safety

Induction of oral bosentan therapy was well tolerated in both patient groups, without signs of decreasing oxygen saturation. One patient without DS experienced severe throat pain and dose was reduced to twice daily 62.5 mg in another patient without DS, who experienced headaches shortly after bosentan initiation, dose was ultimately reduced to 32.5 mg twice daily. A third patient without DS had an asymptomatic increase in liver transaminases (>3 times upper limit of normal), which resolved within 2 weeks after dose reduction, whereupon the 125 mg twice daily dose was resumed without reoccurrence.

4. Discussion

This is the first study reporting on the effect of 4 years of bosentan treatment on exercise capacity, stroke volume and quality of life in adult patients with PAH associated with CHD. We showed a prolonged increase in exercise capacity after 2.5 years of treatment in patients without DS. A beneficial effect was still present up to 4 years of treatment, although failed to reach statistical significance due to low patient numbers. In 2006, the BREATHE-5 study was the first randomised controlled trial which studied the effect of bosentan in patients with Eisenmenger syndrome. Mean improvement of 6MWD in 37 patients was + 53 m after 4 months of treatment and the overall improvement was + 61 m in 26 patients after 10 months of treatment in BREATHE-5 combined with the open-label extension study [6,21]. Two longer-term follow-up studies found a significant increase and maintained effect in 6MWD after 1 year and 2 years of bosentan treatment [9,10]. However, 2 other studies only reported a short term efficacy of bosentan followed by gradual return to baseline after 2 year follow-up [14,15]. Duffels et al. hypothesized that this decline in 6-MWD during treatment might be due to the development of tolerance for bosentan [15]. Our 4 years follow-up study demonstrates that a prolonged effect of bosentan on exercise capacity can be expected in patients with PAH due associated with CHD. We believe clinical stability at 4 year follow-up could be considered successful in a disease that is associated with clinical deterioration.

Additionally, quality of life improved significantly and a remaining effect was shown after 3 years of treatment in patients without DS. Although some quality of life domains remained stable during treatment, others improved significantly. The physical domains role physical and physical functioning increased significantly during bosentan treatment, indicating that patients experienced fewer

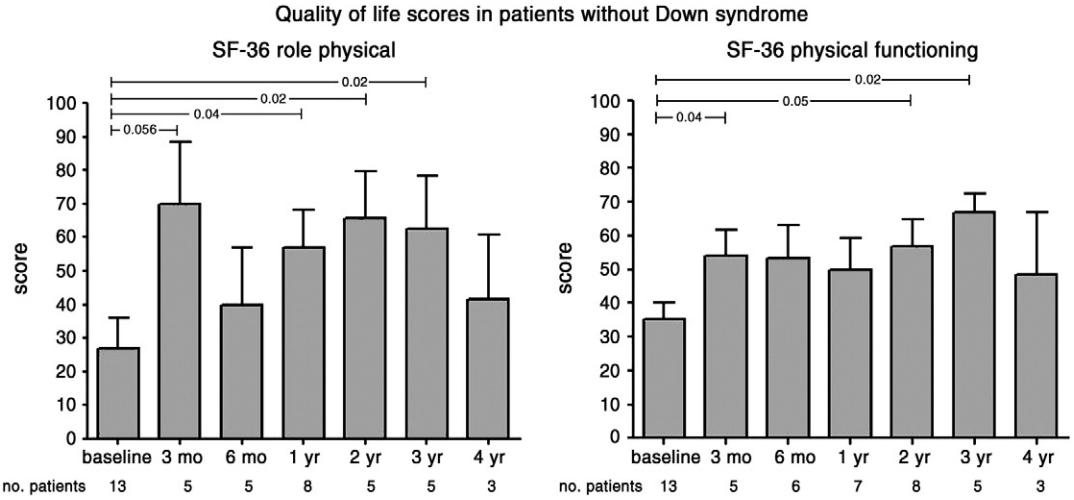

Fig. 4. Quality of life scores in patients without DS. Quality of life scores of the 2 SF-36 domains (a) role physical and (b) physical functioning during follow-up. Data represent the mean score of the SF-36 quality of life questionnaire.

problems at work and during daily activities. In patients with PAH, health related quality of life has been shown to be significantly impaired and evaluation of quality of life is of great importance [22,23]. Moreover, from the patients' perspective, quality of life is one of the most important measures of treatment effect.

We evaluated treatment effect in patients with DS as PAH is particularly common in these patients [24]. In the 2 years follow-up study of Duffels et al., a change on 6MWD was not found due to the disputable validity of the 6MWD in patients with DS [15,20]. The 6MWD appeared to be related to the level of intellectual disability [20]. Therefore, analysis of 6MWD in patients with DS was not performed in the present study. In patients with DS no significant improvement of quality of life could be demonstrated All 8 domains of the SF-36 questionnaire remained stable. The SF-36 questionnaire has not been properly validated in patients with DS making its use for the evaluation of treatment effect questionable. Moreover, echocardiographic parameters remained unchanged during follow-up. Therefore, evaluation of treatment effect remains challenging in patients with DS.

Mean NT-pro-BNP level of the total patient group decreased significantly at 3 months, 6 months and 1 year of follow-up, indicating a positive cardiac effect and lowered right heart decompensation. After 1 year, mean NT-pro-BNP levels returned to baseline. Conclusions on long-term treatment effect after 1 year should be taken with caution due to low patient numbers.

A significant change of 13.5 ml in mean stroke volume was found after 3 years follow-up ($p = 0.02$) in patients without DS. This corresponds to the recent findings of van Wolferen et al. who showed that stroke volume is an important hemodynamic parameter to reflect therapeutic changes during follow-up of PAH [25,26]. In the study of van Wolferen et al., 111 patients with PAH (90% idiopathic PAH and PAH associated with connective tissue disease) were evaluated with cardiac MRI to assess stroke volume at baseline and after 1 year. The minimal important difference was determined using statistical methods and a 10 ml change in stroke volume during follow-up was considered to be clinical relevant [26]. In this respect, the 13.5 ml increase of stroke volume we found in our study can be considered of clinical importance.

Patients with Eisenmenger syndrome are at high risk of death [27] and despite the widespread use of advanced therapies very little evidence on survival benefits is currently available. Survival analysis in the present study showed that after 4 years of follow-up, 20% of the patients died. Dimopoulos et al. found a much lower mortality rate in their retrospective study [28]. Only 2 patients died of a total of 68 Eisenmenger patients (including DS) who received advanced therapy for a median period of 2.4 years (the vast majority of them were in class III or IV at baseline). Two-years overall survival rate was 91% in our study. However, 4 patients died within 6 months after baseline and effect of bosentan might not have been present. Bosentan is not expected to prevent arrhythmic events but rather progressive deterioration and right ventricular failure. In patients younger than 50 years, only 2 died of right ventricular failure. The majority of them died suddenly. Coppus et al. showed that survival of adults with DS is generally lower compared to the general population due to other comorbid factors like dementia and impaired mobility [29]. In the present study, DS was not an independent predictor for survival, most probably due the relatively young patient population. The mean age of patients with DS was 10 years lower than patients without DS (36 vs 46 years). Hypothetically, the underlying congenital defect effects disease progression, however, the post hoc subgroup analysis of the BREATHE-5 study by Berger et al. showed that effect of bosentan treatment was similar in Eisenmenger patients with atrial septal defects and patients with ventricular septal defects [30].

The present study is limited by the lack of a placebo group and the heterogeneity of underlying diagnoses e.g. patients with and without the DS, patients with and without Eisenmenger syndrome, patients with and without closed defects and the variety of defects. Second limitation is the lacking data on time from PAH diagnosis to study inclusion. Most patients had PAH many years before study inclusion. Thirdly, the 6MWT and the SF-36 are not validated in patients with DS. Therefore, definite conclusions on long-term treatment effect of bosentan should be taken with caution in these patients. Another limitation is that not all echocardiographic measurements could be performed in patients with complex cardiac geometry and intra- and inter-observer variability testing was not carried out, however all echocardiograms and analyzing were performed by 1 single observer. Finally, the present study was limited by the lack of hemodynamic data like pulmonary vascular resistance and pulmonary artery pressure. We may assume that PAH diagnosis was made in the past in most patients by right heart catheterisation, except probably for

Table 4
Changes from baseline to end-of-study NYHA class.

Initial minus final NYHA class	−3	−2	−1	0	1	Total
Non Down syndrome	0	8	1	21	4	34
Down syndrome	2	1	4	12	11	30

NYHA; New York Heart Association Class.
NYHA class did not change significantly during follow-up assessed by the Wilcoxon signed-rank test.

some high risk patients with Eisenmenger syndrome, in whom right heart catheterisation was not routinely performed as pulmonary arterial hypertension is clearly evident on echocardiography and these patients are known to be at high risk for complications due to this invasive procedure cardiac catheterisation. Due to this complication risk cardiac catheterisation was not performed to evaluate treatment effect at follow-up.

In conclusion, we demonstrate a prolonged beneficial effect of bosentan treatment on exercise capacity, stroke volume and quality of life in patients without DS. However the mortality rate of 20% of patients after 4 years of follow-up remains high.

Acknowledgements

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

References

[1] Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–537.
[2] Daliento L, Somerville J, Presbitero P, et al. Eisenmenger syndrome. Factors relating to deterioration and death. Eur Heart J 1998;19:1845–55.
[3] Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med 2004;351: 1655–65.
[4] Engelfriet PM, Duffels MG, Moller T, et al. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. Heart 2007;93:682–7.
[5] Duffels MG, Engelfriet PM, Berger RM, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol 2007;120:198–204.
[6] Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 2006;114:48–54.
[7] Keogh AM, McNeil KD, Wlodarczyk J, Gabbay E, Williams TJ. Quality of life in pulmonary arterial hypertension: improvement and maintenance with bosentan. J Heart Lung Transplant 2007;26:181–7.
[8] Peacock A, Naeije R, Galie N, Reeves JT. End points in pulmonary arterial hypertension: the way forward. Eur Respir J 2004;23:947–53.
[9] D'Alto M, Vizza CD, Romeo E, et al. Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect. Heart 2007;93:621–5.
[10] Diller GP, Dimopoulos K, Kaya MG, et al. Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. Heart 2007;93:974–6.
[11] Duffels MG, van Loon RL, Berger RM, Boonstra A, Vonk-Noordegraaf A, Mulder BJ. Pulmonary arterial hypertension associated with a congenital heart defect: advanced medium-term medical treatment stabilizes clinical condition. Congenit Heart Dis 2007;2:242–9.
[12] Schulze-Neick I, Gilbert N, Ewert R, et al. Adult patients with congenital heart disease and pulmonary arterial hypertension: first open prospective multicenter study of bosentan therapy. Am Heart J 2005;150:716.
[13] Sitbon O, McLaughlin VV, Badesch DB, et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. Thorax 2005;60:1025–30.
[14] Apostolopoulou SC, Manginas A, Cokkinos DV, Rammos S. Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. Heart 2007;93:350–4.
[15] Duffels MG, Vis JC, van Loon RL, et al. Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without Down's syndrome. Am J Cardiol 2009;103:1309–15.
[16] Schuuring MJ, Vis JC, Duffels MG, Bouma BJ, Mulder BJ. Adult patients with pulmonary arterial hypertension due to congenital heart disease: a review on advanced medical treatment with bosentan. Ther Clin Risk Manage 2010;6: 359–66.
[17] van Loon RL, Hoendermis ES, Duffels MG, et al. Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: does the beneficial effect persist? Am Heart J 2007;154:776–82.
[18] Duffels MG, Vis JC, van Loon RL, et al. Down patients with Eisenmenger syndrome: is bosentan treatment an option? Int J Cardiol 2009;134:378–83.
[19] American Thoracic Society statement. Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.
[20] Vis JC, Thoonsen H, Duffels MG, et al. Six-minute walk test in patients with Down syndrome: validity and reproducibility. Arch Phys Med Rehabil 2009;90:1423–7.
[21] Gatzoulis MA, Beghetti M, Galie N, et al. Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study. Int J Cardiol 2008;127:27–32.
[22] McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. Qual Life Res 2006;15:103–15.
[23] Zlupko M, Harhay MO, Gallop R, et al. Evaluation of disease-specific health-related quality of life in patients with pulmonary arterial hypertension. Respir Med 2008;102:1431–8.
[24] Vis JC, Duffels MG, Winter MM, et al. Down syndrome: a cardiovascular perspective. J Intellect Disabil Res 2009;53:419–25.
[25] Roeleveld RJ, Vonk-Noordegraaf A, Marcus JT, et al. Effects of epoprostenol on right ventricular hypertrophy and dilatation in pulmonary hypertension. Chest 2004;125:572–9.
[26] van Wolferen SA, van de Veerdonk MC, Mauritz GJ, et al. Clinical significant change of stroke volume in pulmonary hypertension. Chest 2011;139:1003–9.
[27] Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. J Heart Lung Transplant 1996;15:100–5.
[28] Dimopoulos K, Inuzuka R, Goletto S, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 2010;121:20–5.
[29] Coppus AM, Evenhuis HM, Verberne GJ, et al. Survival in elderly persons with Down syndrome. J Am Geriatr Soc 2008;56:2311–6.
[30] Berger RM, Beghetti M, Galie N, et al. Atrial septal defects versus ventricular septal defects in BREATHE-5, a placebo-controlled study of pulmonary arterial hypertension related to Eisenmenger's syndrome: a subgroup analysis. Int J Cardiol 2010;144:373–8.